Prolonged Neonatal Jaundice in Cystic Fibrosis

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Valman, H. B., France, N. E., and Wallis, P. G. (1971). Archives of Disease in Childhood, 46, 805. Prolonged neonatal jaundice in cystic fibrosis. Four patients with cystic fibrosis developed prolonged obstructive jaundice starting in the newborn period. Obstructive biliary cirrhosis was shown post mortem in one of them who died at 5 months from pneumonia, while another dying at 8 years had an histologically normal liver at necropsy. The two survivors were jaundiced for 6 months and 5 weeks respectively, before making a clinical recovery, and in both liver biopsy at the height of the jaundice showed bile stasis.

Meconium ileus was present in half of all recorded cases of cystic fibrosis with prolonged neonatal jaundice. Jaundice is probably due to extrahepatic biliary obstruction from bile of increased density, with secondary intrahepatic bile stasis.

Increased density of the bile was noted in the earlier descriptions of cystic fibrosis (Andersen, 1938), while focal biliary fibrosis associated with concretions in the intrahepatic bile ducts is a frequent finding (Bodian, 1952; Di Sant’Agnese and Blanc, 1956). Such cirrhotic lesions are few or absent in the newborn period but become progressively more frequent and severe with increasing age (Alagille and Le Tan Vinh, 1961). In view of the high bilirubin load in the neonatal period, the small calibre of the bile ducts, and the frequency of glandular changes in the extrahepatic bile ducts in cystic fibrosis, it might be expected that these neonates would show a high incidence of obstructive jaundice. On the contrary, only six such patients have been described previously (Gatzimos and Jowitt, 1955; Bernstein et al., 1960; Shier and Horn, 1963; Bachand, 1967; Kulczycki, 1967; Talamo and Hendren, 1968).

Case Reports

Case 1. A boy was delivered normally at term of a primiparous mother whose blood group was O Rh negative. He weighed 2.265 kg at birth. Progress was satisfactory until 22 days when slight jaundice and pale stools were noted. At 7 weeks, there was a moderate degree of jaundice with white stools and dark urine though the liver and spleen were not enlarged. The feet and legs were oedematous.

Investigations. Haemoglobin 7.3 g/100 ml, blood group O Rh positive, direct Coombs test negative.

Urinary urobilinogen negative; urinary bile pigments positive. Stool bile pigments negative. Serum bilirubin direct reaction strongly positive, indirect 8·4 mg/100 ml; alkaline phosphatase 18·1 KA units/100 ml, serum cholesterol 300 mg/100 ml. Thymol turbidity and colloidal gold test normal. Total serum proteins 3·75 g/100 ml. No trypsin was found in two specimens of stool or in duodenal aspirate.

Progress. The oedema disappeared promptly after transfusion of blood and plasma, but the stools remained offensive and pale throughout his life. His weight never exceeded 3·545 kg. At the age of 18 weeks he developed pneumonic consolidation of the right upper lobe, which failed to respond to antibiotics and he died at 22 weeks.

Necropsy findings. The liver was deep green with a finely granular surface, firm consistency, and a clear lobular pattern on the cut surface. Microscopically, there was biliary cirrhosis with proliferation of bile ducts (Fig. 1). Plugs of bile occupied many centrilobular canaliculi and bile ducts. The gall bladder was small, filled with faintly bile-stained, tenacious mucus, and microscopically showed considerable dilatation of mucous glands. The hepatic and common bile ducts were patent throughout, but the latter was narrow at the ampulla of Vater. The pancreas showed typical cystic fibrosis and there was dilatation of the mucous glands of the upper air passages, glands of Brünner, and appendix. The upper and lower lobes of the right lung showed bronchopneumonia associated with typical cells of cytomegalic inclusion disease. Similar cells were present in the glands of Brünner and in the edge of a small ulcer of the first part of the duodenum, but none was found in the bile ducts or at the ampulla.

Received 1 June 1971.
Fig. 1.—Case 1. Liver showing biliary cirrhosis with accumulation of bile in proliferated bile ducts (H and E × 75).

Case 2. This female child was delivered normally at term after the mother’s first pregnancy. On the second day of life she developed signs of intestinal obstruction, and laparotomy at 50 hours showed meconium ileus and volvulus of the midjejunum. A length of jejunum was resected and an ileostomy was fashioned by the Bishop-Koop procedure. It was estimated that about 90 cm of small intestine remained. Intravenous fluid therapy was continued until the age of 14 days, but 2 days after starting to take a diluted milk mixture she began to pass loose, white stools. Intravenous fluids were restarted and later a dilute milk mixture with glucose and casein hydrolysate was given. Jaundice was noticed first at the age of 21 days when the serum bilirubin was 5.9 mg/100 ml (3.9 mg/100 ml conjugated) and the total white blood cell count was 24,000 per mm³ (metamyelocytes 3%, stab cells 18%, neutrophils 50%, eosinophils 2%, basophils 1%, lymphocytes 25%, monocytes 1%). High doses of intramuscular ampicillin and cloxacillin were administered for probable sepsicaemia. At 28 days the serum bilirubin level had risen to 15.3 mg/100 ml, the liver extended 4.5 cm below the right costal margin, and the spleen was just palpable. Cytomegalovirus was grown from the urine at 7 weeks (Dr. J. A. Dudgeon). As the serum bilirubin remained at about the same level, laparotomy for

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age at Onset of Jaundice</th>
<th>Duration of Jaundice</th>
<th>Biopsy</th>
<th>Necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatzimos and Jowitt (1955) Case 1</td>
<td>4 dy Newborn</td>
<td>Until death at 20 dy ?</td>
<td>Bile stasis (10 dy)</td>
<td>Postnecrotic cirrhosis to pericholangitis</td>
</tr>
<tr>
<td>Bernstein et al. (1960) Case 2</td>
<td>Before 10 dy</td>
<td>Until death at 40 dy</td>
<td>Biliary cirrhosis (7 wk)</td>
<td>Focal biliary cirrhosis</td>
</tr>
<tr>
<td>Shier and Horn (1963)</td>
<td>2 dy</td>
<td>Until 2-3 wk after flushing common bile duct at 7 wk</td>
<td>Mild biliary cirrhosis (3 mth)</td>
<td></td>
</tr>
<tr>
<td>Bachand (1967)</td>
<td>1st dy</td>
<td>40-50 dy</td>
<td></td>
<td></td>
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<tr>
<td>Kulczycki (1967)</td>
<td></td>
<td></td>
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<tr>
<td>Talamo and Hendren (1968)</td>
<td></td>
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<tr>
<td>This paper</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case 1</td>
<td>3 wk</td>
<td>Until death at 5 mth</td>
<td></td>
<td>Obstructive biliary cirrhosis</td>
</tr>
<tr>
<td>Case 2</td>
<td>3 wk</td>
<td>6 mth</td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Case 3</td>
<td>Birth</td>
<td>3 mth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>3 dy</td>
<td>5 wk</td>
<td></td>
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- = Not recorded.
possible atresia of the bile ducts was performed at 9 weeks of age. The liver was enlarged and greenish-brown but had a smooth surface and normal consistency. Microscopically it showed plugs of bile in many canaliculi and increased bile pigment in parenchyma cells and Kupffer cells; lymphocytes were increased in the portal tracts but there was no evidence of cirrhosis (Fig. 2). Solid, dark green bile was removed with forceps from the distended gall bladder, which was washed out with a solution of pancreatin. No radio-opaque material was seen in the bile ducts of duodenum on cholangiography, suggesting that the cystic duct and probably the common bile duct were blocked. In spite of the introduction of saline solution into a cholecystostomy on several occasions after operation, the stools remained white. However, at the age of 11 weeks the serum bilirubin levels fell to 4-4 mg/100 ml and remained at about that level for the next 10 weeks. At 14 weeks, injection of urografin into the cholecystostomy tube demonstrated patency of the cystic, hepatic, and common bile ducts, and at 5 months bile appeared in the stools, at first intermittently and then persistently, with associated fall of the serum bilirubin level to normal and a rapid gain in weight. She had two episodes of bronchi- tis at 6 months when a chest x-ray showed slight thickening of the bronchial walls. The sweat sodium was

<table>
<thead>
<tr>
<th>Evidence of Cytomegalovirus Infection</th>
<th>Meconium Ileus</th>
<th>Alkaline Phosphatase</th>
<th>Floculation Tests</th>
<th>Serum Cholesterol (mg/100 ml)</th>
<th>SGOT (μM/min per l.)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Died at 20 dy</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Survived</td>
</tr>
<tr>
<td>−</td>
<td></td>
<td>6.7 Bodansky units</td>
<td>Normal</td>
<td>192</td>
<td>−</td>
<td>Died at 3 yr</td>
</tr>
<tr>
<td>−</td>
<td></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>62 (SGPT)</td>
<td>Died at 40 dy</td>
</tr>
<tr>
<td>−</td>
<td></td>
<td>30 KA units</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>Survived</td>
</tr>
<tr>
<td>No bodies in urine</td>
<td>+</td>
<td>25 KA units</td>
<td>−</td>
<td>−</td>
<td>155</td>
<td>Survived</td>
</tr>
<tr>
<td>Bodies in lungs and duodenum</td>
<td></td>
<td>−</td>
<td>18.1 KA units</td>
<td>300</td>
<td>−</td>
<td>Died at 5 mth</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>−</td>
<td>12 KA units</td>
<td>190</td>
<td>450</td>
<td>Survived</td>
</tr>
<tr>
<td>Positive urine culture</td>
<td></td>
<td>−</td>
<td>16 KA units</td>
<td>−</td>
<td>−</td>
<td>Died at 8 yr</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>−</td>
<td>16.7 KA units</td>
<td>385</td>
<td>−</td>
<td>Survived</td>
</tr>
</tbody>
</table>
106 mEq/l. At 11 months she was on the 10th centile for height and weight, had 4 teeth, could stand unaided, and could say 2 words.

**Case 3.** A female, normal delivery at term to a primiparous mother; birthweight 2·325 kg. She passed meconium of normal colour but thereafter all stools were white. 4 weeks after birth she had gained only 30 g in weight and slight jaundice was noted, though the liver and spleen were not enlarged. No trypsin was demonstrated in stools or duodenal juice.

**Investigations.** Serum bilirubin 5·7 mg/100 ml (3·5 mg/100 ml conjugated); alkaline phosphatase 16 KA units/100 ml. Total serum protein 4·5 g/100 ml (albumin 3·0 g, globulin 1·5 g); flocculation tests normal; bile pigments present in urine; no stercobilin in stool.

**Progress.** At the age of 9 weeks she developed right upper and middle lobe pneumonic consolidation which completely cleared radiologically after five weeks after a course of oral erythromycin and neomycin aerosol. Jaundice and pale stools persisted until she was 12 weeks old when bile appeared in the stools and the serum bilirubin level fell to 1·4 mg/100 ml. Her condition improved rapidly, and at 15 weeks her weight was 3·91 kg. She subsequently developed recurrent lower respiratory tract infection and died at the age of 8⅓ years from supplicative bronchopneumonia. At necropsy the liver was histologically normal, and advanced changes of cystic fibrosis were found in the pancreas.

**Case 4.** A male, normal full-term delivery; birthweight 2·95 kg. On the third day of life he developed signs of intestinal obstruction which was shown at laparotomy to be due to meconium ileus and volvulus necessitating resection of ileum. Jaundice was present postoperatively and persisted while pale stools were noted first at 10 days. The serum bilirubin rose gradually reaching 15·6 mg/100 ml (indirect 4·6 mg/100 ml) at 28 days. Needle biopsy of the liver at 33 days showed cholestasis only. He was treated with prednisone 15 mg daily and after six days the serum bilirubin level had fallen to 4·3 mg/100 ml (indirect 1·1 mg/100 ml). At the age of 2 months his weight was 3·175 kg, but by 4 months he had reached the 25th centile for weight and remained on this centile. From 3 to 5 months the spleen was palpable but at no stage was the liver enlarged. At 4 years he developed pneumonic consolidation for the first time. Sweat sodium was 110 mEq/l., serum alkaline phosphatase 18 KA units/100 ml, serum bilirubin, flocculation tests, and SGPT were normal.

**Discussion**

Accumulation of thick bile in the extrahepatic biliary system was observed by Bachand (1967) and Kulczycki (1967) in two infants with prolonged obstructive jaundice and cystic fibrosis. The obstruction in Bachand’s patient was removed surgically but he died at 40 days with haemorrhagic complications. Kulczycki’s patient was treated by flushing the bile ducts with saline; this was followed by rapid reduction of jaundice and general clinical improvement. In Case 2, solid green bile was found in the gall bladder at laparotomy, a condition only once previously described in a baby dying with cystic fibrosis (Esterly and Oppenheimer, 1962); in addition the extrahepatic bile ducts appear to have been blocked by thick bile which flushing failed to remove. These observations suggest that prolonged jaundice, at least in some patients, is due mainly to obstruction of the extrahepatic bile ducts by thick bile, and it is probable that this leads to intrahepatic bile stasis. Biopsy of the liver taken at the height of the jaundice in Cases 2 and 4 showed bile stasis similar to that described by Gatzimos and Jowitt (1955) and Bachand (1967), while Talamo and Hendren (1968) showed such changes some weeks after the jaundice had faded. These histological features do not differ essentially from those described by Haas (1968) in infants not obviously suffering from cystic fibrosis. Though focal biliary cirrhosis is found post mortem in over a third of all patients dying with cystic fibrosis (Alagille and Le Tan Vinh, 1961), it is uncommon under the age of 6 months and is probably not related to biliary stasis. On the other hand, the cirrhosis in Case 1 could be considered to be the direct result of biliary obstruction. The incidence of meconium ileus in all recorded patients (Table) is about five times the expected incidence in cystic fibrosis, and this may be a factor in the aetiology of the jaundice.

Infection by cytomegalovirus can cause prolonged obstructive jaundice in infancy. Typical inclusion bodies were present in the lungs and gut of Case 1 and the virus was isolated from the urine of Case 2 but in neither patient was there histological evidence of cytomegalovirus hepatitis. It is conceivable that jaundice was the result of cytomegalic involvement of the bile ducts of Case but this was not demonstrated post mortem. As the virus is commonly present in the tissues of patients dying with debilitating diseases such as cystic fibrosis (Blattner, 1969), it is probable that this infection was incidental.

Liver function tests are of little value in differentiating neonatal hepatitis and extrahepatic biliary obstruction (Thaler and Gellis, 1968). If jaundice persists, laparotomy is usually undertaken at about 6 weeks of age when liver biopsy and operative cholangiography through the gall bladder are performed. If the patient is known to suffer from
Prolonged Neonatal Jaundice in Cystic Fibrosis

809

References


We thank Dr. I. M. Anderson and Dr. M. B. Mears for permission to publish the clinical details of Cases 1 and 2, Mr. V. A. J. Swain for his laparotomy report in Case 2, Dr. M. J. Wilmer for her encouragement, Mrs. F. M. Byron for technical assistance.

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cystic fibrosis there are three possible lines of management: (1) conservative, (2) flushing of extrahepatic bile ducts at laparotomy, and (3) steroid therapy. These are illustrated by the present series. Case 3 was managed conservatively throughout and her liver was histologically normal at her death eight years later. Though Kulczycki (1967) was successful in clearing the bile ducts by flushing, this procedure failed in Case 2 and thereafter she was treated conservatively; jaundice persisted for six months after which she made a rapid clinical recovery and two years later had no clinical or biochemical evidence of liver disease. Conservative treatment of Case 1 was unsuccessful and she died of pneumonia at 5 months when biliary cirrhosis was demonstrated at necropsy. The effect of steroids is uncertain and they may only convert bilirubin into a colourless substance without affecting the histological appearance of the liver (Sherlock, 1968). Treatment with steroids in Case 4 was followed within a week by a dramatic fall of the serum bilirubin level. Talamo and Hendren (1968) treated their patient similarly but jaundice persisted for about 50 days. Our experience suggests that, while surgical intervention may be necessary in some cases, a more conservative approach is frequently successful.
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Arch Dis Child 1971 46: 805-809
doi: 10.1136/adc.46.250.805

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